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Evidence-based Policies? The Covid-19 Pandemic and the Prospects of Evidence Integration

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RESUMEN

Para justificar sus políticas durante la pandemia de Covid-19, los gobiernos han implícitamente recurrido, sobre todo en las fases iniciales, a una versión sesgada de la 'medicina basada en la evidencia`, una filosofía de la medicina que se basa especialmente en la evidencia computacional y estadística. Este enfoque muestra al menos una debilidad relevante: ignora gran parte de las evidencias clínicas y mecanicistas y su potencial contribución a la comprensión y la gestión de le enfermedad. Argumentamos que un enfoque pluralista de la evidencia, centrado en la integración, podría apoyar mejor la lucha contra esta y futuras pandemias.

PALABRAS CLAVE: *Covid-19, pandemia, medicina basada en la evidencia, integración en la evidencia, explicación mecanicista*.

ABSTRACT

In order to justify their policies during the Covid-19 pandemic, governments have implicitly appealed, especially in the early phases, to a biased 'evidence-based' philosophy of medicine heavily relying on computational and statistical evidence. This approach shows an important weakness: it largely ignores clinical and mechanistic evidence that could greatly contribute to the understanding and management of the disease. We shall argue that a pluralistic approach to evidence focused on integration could better support the fight against this and future pandemics.

KEYWORDS: *Covid-19, Pandemic, Evidence-Based-Medicine, Evidence Integration, Mechanistic Explanation*.

I. PANDEMICS AND PUBLIC HEALTH: A LITMUS TEST FOR GOVERNMENTS

The Covid-19 pandemic is an unprecedented litmus test for national governments and international institutions. It has uncovered, among other frailties, the fragility of our health systems, the opacity of the ethi-

cal framing of governments' responses as well as flaws in democratic processes. Even though governments' responses have varied, a common element in their political narratives can be identified. Governments have continuously appealed to the authority of science and the role of evidence in order to justify their response to the Covid-19 pandemic. At the very start, it was acknowledged that the evidential basis for governments' policy decisions was meagre. Indeed, the scarcity of the evidential basis was a chief factor justifying extreme precautionary measures such as lockdowns. Concomitantly, governments have continuously stressed that their policy responses are 'evidence-based'. Independently of whether the adoption of a precautionary approach is politically and ethically justifiable in conditions of uncertainty characterised by paucity of evidence, there remains an underlying problem concerning the very nature of the evidence that should be used in a medical context in order to devise non-pharmaceutical and medical interventions. After all, different biomedically-relevant disciplines explicitly or implicitly use different methodologies and understand causality in different ways. As a consequence, this variability in epistemological and ontological commitments might imply the adoption of different models of disease. The question is thus raised concerning whether particular disciplines should be given a primary role in informing evidence-based policies and whether the prioritisation of certain kinds of evidence is justified. The philosophy of medicine is instrumental in order to uncover the implicit evidential strategy underlying governments' official narrative. We think that the current pandemic offers a significant opportunity to provide such analysis. This is the aim of the present paper.

Let us first characterise the complexity of the current pandemic by providing a representation of the variety of medical questions that need to be answered. What needs to be known in order to inform appropriate and comprehensive evidence-based policy responses is, ideally, reliable information about the origin of the virus and of the human infection, the way in which it is transmitted between humans, the way in which it infects humans and the way in which humans respond to infection. Schematically, we could categorise the four medically relevant aspects of the pandemic as: origin, transmission, organismal infection, organismal response (Figure 1). Three important general issues should be highlighted in the present context.

First of all, different scientific disciplines provide the evidential basis for understanding the four medically relevant aspects of the pandemic. For instance, origin studies require genomic and virological evidence, trans-

mission dynamics are modelled by epidemiology, infection is approached by physiology and clinical studies, while response is the province of immunology. Thus, a variety of evidences are relevant to conceptualise and understand these different but interrelated aspects of the pandemic.

Secondly, note that all the evidence potentially affects the way in which medical questions are approached, with implications concerning how appropriate responses should be devised. For instance, if we were to know with precision when the human infection by Sars-Cov-2 started and we had detailed information about its transmission dynamics, this would potentially impinge on our understanding of populational immunity.

Thirdly, despite extensive ignorance concerning all these medically relevant aspects of the pandemic still impairs interventions, the evidential basis has been continuously growing in the past months. Thus, common sense dictates that the entire panoply of studies constituting this growing evidential basis should ideally inform appropriate evidence-based policies.

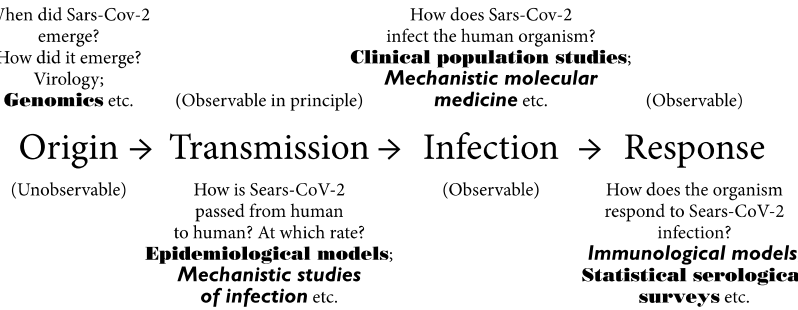


Figure 1 – The four interrelated medically relevant aspects in the Covid-19 pandemic case. An answer to each of these questions would inform appropriate and comprehensive evidence-based policy responses. At least transmission, infection and response can be approached through a variety of 'statistical' (bold type) and 'mechanistic' (italics) approaches.

We shall start (II) by illustrating how the varieties of evidence available in current medical science are classified and ranked, the supposed advantages of hierarchisation and the critiques and alternatives proposed in the literature. Based on these considerations, we (III) suggest a way to categorise evidence in the case of the current pandemic and argue that an efficient management of the emergency requires an approach integrating evidences

rather than prioritising them. Finally, we extrapolate (IV) some conclusions from the Covid-19 pandemic case tailored to improve policy making.

II. Evidence-Based Medicine: Biostatistical Evidence and Models Vs. Mechanistic and Clinical Knowledge

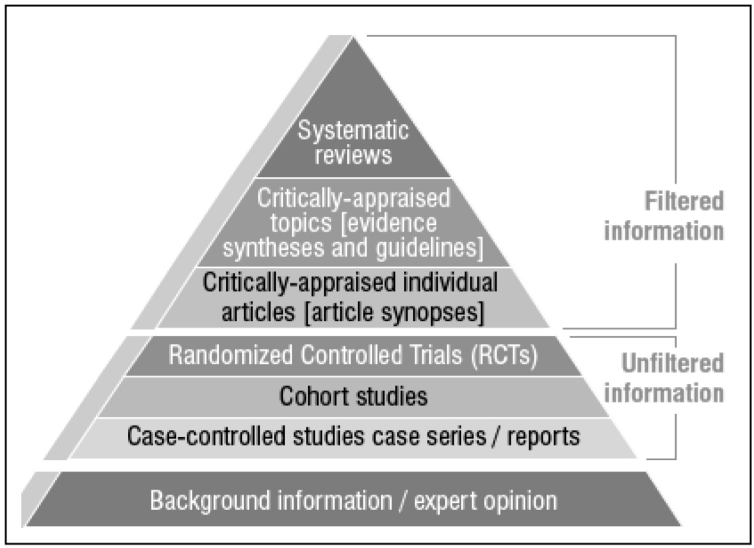
Medical research has a cognitive and an action-oriented goal [Russo and Williamson (2007)]. A variety of disciplinary sources generate a multiplicity of kinds of evidence available to approach these goals, ranging from epidemiology and biostatistics to bioinformatics and genomics, from clinical practice and immunology to biochemistry and virology. Evidence gathering methods also cover a wide range: from randomised clinical trials (henceforth RCTs) to individual case reports, from laboratory experiments to epidemiological studies, from experts' opinions to mathematical models. All these disciplines and methods supply different kinds of information and generalisations for policy action. Selecting, interpreting and amalgamating such abundance of evidence in order to understand which variables are relevant to produce a desired output, and through which casual pathways, is a main challenge and an open issue for the health sciences [Stegenga (2014)]. The problem is particularly relevant in emergency situations such as the Covid-19 pandemic, whereby time limitations and resource constraints require clear and quickly acquired data to inform decision makers. Given this variety of evidences, governments have thus significant leeway in deciding to base their policies on selected epistemological resources rather than others, in following the advice of a subset of so-called 'experts', in dismissing certain policies in the light of 'insufficient' evidence etc. The philosophy of medicine should play a fundamental role in the critical evaluation of this selection, which otherwise risks, at best, being idiosyncratically changed or, at worst, to be guided by spurious interests.

A widely used heuristic method to order kinds of evidence is to rank them with respect to the rigour of the gathering methodology, which is inversely proportional to their probability of suffering systematic bias [Stegenga (2014)]. More than 80 such rankings, known as 'evidence hierarchies', are available, among them the U.S. Preventive Services Task Force (USPSTF), the Oxford (UK) CEBM Levels of Evidence, and the GRADE (Grading of Recommendations Assessment, Development and Evaluation).[1] Evidence hierarchies are a main tool in evidence-based medicine (henceforth EBM), promoting "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of

individual patients" [Sackett et al. (1996), p. 71]. Emerged in the 90s, EBM privileges statistical evidence as 'best' in addressing a variety of medical situations over (supposedly) biased and observer-dependent clinical evidence or evidence of pathophysiological mechanisms of organismal response to disease, produced by clinical practitioners appealing to probably outdated theories and models [Davidoff et al. (1995)]. The current emphasis on statistical research, 'data-driven' science and medical informatics, and its collateral effect of dispensing of observational, clinical and mechanistic evidence, come from this intransigent empiricist focus.

Meta-analyses of large-scale epidemiological studies are usually placed at the top of hierarchies, followed by RCTs; while case reports and expert opinions are usually placed at the bottom. A main distinction behind hierarchies has to do with the systematicity of reviews. Meta-analyses are systematic in that they are based on focused clinical questions, clearly stated sources and search strategy, thus offering qualitative summary with statistical synthesis. The scope of narrative reviews such as expert opinions or individual case studies is often broader, with the implication that they might suffer from bias in their sources and offer only qualitative results [Cook & Mulrow & Haynes (1997)]. Figure 2-TOP shows a typical evidence hierarchy.

Hierarchies and their rationale have been thoroughly criticised [Petticrew & Roberts (2003); Clarke et al. (2013)]. Stegenga (2014) underlines that actual studies might be poor applications of ideal methodologies (e.g., some RCTs are poorly reliable), that rankings should depend on the type of hypothesis tested (e.g., the potential harm of an intervention is usually discovered through observation of individual cases, not RTCs), and that they are based on few parameters (basically randomisation), being as a consequence very 'crude' tools. Moreover, hierarchies do not provide ways to amalgamate evidences from different sources, but just suggest ignoring those at the bottom. This fundamental point is developed in section 3. Alternative classifications have been proposed. Bluhm (2005), p. 535, suggests replacing the hierarchy of evidence "by a *network* that takes into account the relationship between epidemiological and laboratory research". Petticrew and Roberts (2003) build an evidence *matrix* where each evidence-gathering method is assigned a score from 1 to 3 in several different respects (effectiveness, safety, appropriateness): so that, say, RCTs score high in safety but low in acceptability by patients. Cartwright and Hardie (2012) recur to evidence pyramids (Figure 2-BOTTOM).



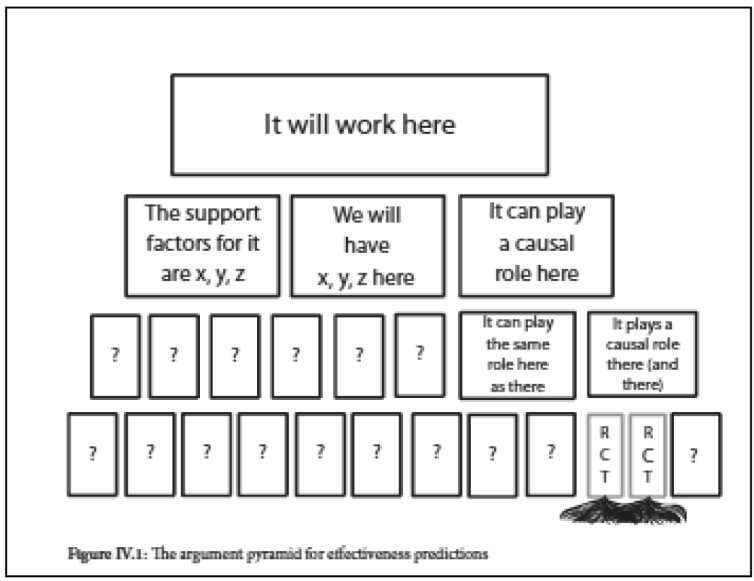


Figure 2 – (TOP) hierarchy of evidence provided by the National Health and Medical Research Council (NHMRC) [source *https://canberra.libguides.com/c.php?g=599346&p=4149721*]. (BOTTOM) Evidence pyramid showing the (low) confidence warranted by a single RCT to a policy claim [from Cartwright and Hardie (2012)].

The top and the bottom layers of the evidence hierarchies are occupied by families of methods (roughly) identifiable, respectively, with a probabilistic and a mechanistic approach. Both kinds of methods are required to generate evidence: probabilities show that causes might affect effects, while mechanisms explain the putative nature of the causal pathway [Russo & Williamson (2007), Clarke et al. (2014), Grüne-Yanoff (2016)]. The probabilistic approach (underlying, e.g., systematic reviews, RCTs) looks for statistical relationships among the variables of a chosen system (e.g., a population), so that its behaviour can be predicted and manipulated, without caring much about the nature of the putative causal relationships: its results (e.g., RCT data) are supposedly theory-free. Conversely, the mechanistic approach (underlying, e.g., laboratory experiments, theoretical arguments), endorses the view that causal connections are the result of physical processes and not just probabilistic correlations: it explains and predicts by studying how the system's entities and activities shape its behaviour [Illari & Williamson (2012)]. Both interpretations are defended and criticised for specular reasons.

Populations, organisms, cells or physiological pathways are complex systems decomposable in different ways and whereby a number of entities with differing activities simultaneously interact and produce a large number of phenomena of biomedical interest. Identifying relevant variables, isolating them from interferences, and classifying them as causes or effects are elements of a titanic task, and each approach is especially good at handling some of these elements and bad at handling others. Pluralistic approaches suggest amalgamating, rather than ranking, evidence of different kinds [Russo & Williamson (2007), Illari (2011)]. Mechanistic evidence can, for example, clarify whether a statistical regularity reflects a causal relationships between two variables A and B, or whether it is accidental, or even due to a confounding variable C influencing both A and B and thus causing a spurious association.[2] Mechanisms, moreover, support the translation of a successful policy to a different environment (e.g., a RCT to a real population, or a population study to an individual case), something that a crude statistical association can hardly do [this is known as the 'external validity' problem, cf. Victora & Habicht & Bryce (2004)]. Finally, mechanistic hypotheses are needed for the design of probabilistic studies, to identify which variables are relevant, etc. [Clarke et al. (2014)]. Probabilistic evidence can, on the other hand, help detecting and avoiding the problem of masking [Illari (2011)], or the contemporaneous existence of several mechanisms linking variable A to variable B. If increasing A reduces B according to a mechanistic model, it might well increase B due to a second, not considered, mechanism. Some

authors deny any distinction between mechanistic and probabilistic evidence claiming that, ultimately, the methods, scope and level of analysis of statistical and mechanistic approaches have a common core - focusing instead on whether the evidence indicates 'difference-making': if not, neither probabilistic nor mechanistic evidence is useful for policy extrapolation [Marchionni and Rejiula (2018)]. Independently of whether evidence type, evidence gathering method and object of evidence are conceptualized and discriminated by pluralistic approaches, we shall emphasise the importance of evidential integration on the generation, refinement and testing of the hypotheses formulated by using different methodologies (section III.5).

III. Prioritisation vs. Integration of Evidences

As we anticipated in section 1, many disciplines contribute to the four medically relevant aspects of the pandemic. An overwhelming amount of data is thus available, provided by governmental health agencies, interpreted by teams of experts and used to fuel mathematical modelling to support policy making. More than 36.000 documents are available on the WHO website,[3] of which less than 10% are classified according to EBM hierarchies. Of these, almost 1/3 are 'case studies' (a type of evidence at the bottom of evidential hierarchies), while controlled clinical trials (a type of evidence at the top of evidential hierarchies) represent just 5% of the total. We categorise some of this abundant information by distinguishing computational, statistical, observational and mechanistic kinds of evidence. Our aim is not to create a new exhaustive classification of evidential kinds (see section II and Higgins JPT 2009). The more modest aim is to refer to kinds of evidence available for Covid-19 as a guide for substantiating our argument that their relative weaknesses could, through amalgamation, provide a more solid basis for policy making [Illari (2011)]. The commonsense approach we propose is that to privilege one kind of evidence over others as a panacea for protecting the human population is meaningless. We shall argue that the current pandemic highlights the fundamental point that amalgamation and integration of evidence kinds should be the driving force behind any governments' attempt to devise non-pharmaceutical and medical interventions, being they tailored to reduce contagion, finding medical treatments or understanding immunity.

III.1 *Computational Evidence*

Governments' initial policy reactions to the pandemic were focused on managing (either delaying, mitigating or suppressing) transmission by

heavily relying on mathematical modelling. The understandable reason is that we knew almost nothing about organismal infection and response, while origin hypotheses are to this day speculative. As a consequence, more than 40 epidemiological models were already available at the beginning of April [Jefferson and Heneghan (2020)]. Mathematical epidemiology provides statistical evidence that policy interventions of specific kinds will have predictable effects, more often than not within very significant thresholds. The dynamics of the spread of the virus and its effects on the population in terms of morbidity and death are modelled without focusing on the biological complexity of the individual organisms and their specific and idiosyncratic responses. As a consequence, individual organisms are ascribed a probability of getting infected, of ending up in hospital and of dying [these are known as SIR models, cf. Kermack, and McKendrick (1927) for the original model or Harko, Lobo and Mak (2014) for advanced applications to pandemics].

Models are powerful tools but, of course, have limitations. One must not forget that their semantic is context-dependent. The reliability of a model depends on how its software has been conceived and built. Its simulations can be considered significant insofar as the data it is fuelled by is reliable. This is the well-known GIGO, or 'Garbage-In-Garbage-Out' problem: the limitations of the input data should be clearly stated and sensitivity analysis performed, which has not occurred in the case of most of the Covid-19 models [Jefferson and Heneghan (2020)]. All of these limitations are evident when we consider the main epidemiological model for Covid-19, the Imperial College London simulator, which has triggered the U-turn in UK's policy by forecasting half a million deaths in case no non-pharmaceutical interventions were taken. Firstly, its objectives are not clearly stated (i.e., software specification is lacking). Secondly, the significance and reliability of its predictions is questionable as the input data is itself questionable. Finally, it does not comply with software engineering standards [Horner and Symons (2020), Singh Chawla (2020)]. This lack of transparency is frustrating as it poses an obstacle to the policy ideal of informing scientific community and public at large. Particularly significant have been the use of putatively inflated variables [e.g., infection fatality rate, cf. Verity et al. (2020)] and the underestimation of other variables (e.g., percentage of asymptomatic patients acting as vectors of contagion). These are not idle issues because simulations have not only played a prominent role in inducing lockdowns, but still play a pivotal role in policy decisions concerning easing restrictions and reintroducing local lockdowns. Ultimately, computational evidence is – independently of the quality of the modelling substantiating it – of limited importance in

finding a way out in the management of the disease: the medical value of non-pharmaceutical interventions can only go as far as either curbing contagion (through tighter social restrictions) or even effectively fostering population immunity (through social restrictions relaxation).

III.2 *Statistical evidence*

The emphasis on quantitative statistical research, meta-analysis, 'data-driven' science and medical informatics at the root of orthodox evidence-based medicine comes from an arguably intransigent empiricist focus [Cohen et al. (2004)]. Getting rid of theory is one aspect of this endeavour. Getting rid of rich interpretations of causality is another (in the Humean spirit of dismissing as unscientific reference to the unobservable processes underlying medically relevant causal relations).[4] The two aspects are interrelated and tailored to downplay theory-rich observational, clinical and mechanistic studies that make reference to putative genuine causal relations rather than mere statistical correlations. There is no denying that statistical studies and meta-analysis of several observational and clinical studies are biomedically crucial. But to extrapolate an over-arching philosophy of medicine from statistical correlations remains philosophically blind-sighted. The flimsy empiricist basis of orthodox evidence-based medicine has already been criticised, for instance by Russo & Williamson (2007) and Clarke et al. (2013). We concur with the pluralistic and integrative ethos of such criticisms. In this context, we would like to highlight two medically relevant examples pointing in the same direction: biomedicine as a multi-disciplinary area of studies should be also informed by theoretical insights and mechanistic reasoning [Marchionni & Reijula (2018)] and should also aim at providing mechanistic evidence in favour of medical interventions.

The first drug that has been shown to reduce Covid-19 mortality is dexamethasone, which appears to stop the damage of the severe immune reaction (i.e., 'cytokine storm') often observed clinically in severely ill patients. A RCT was run and the drug found effective. This seems a very powerful argument for prioritising statistical evidence coming from RCTs. However, the insight for running the RCT was inevitably theoretical. In fact, it is known that steroids suppress the immune system, which could provide some relief for patients whose lungs are ravaged by an over-active immune response.[5] In this case, a theoretical insight temporally prior to the decision to perform RCTs shows how statistical evidence is parasitic on theoretical knowledge.

An instructive example of misapplication of statistical thinking is race medicine, the hypothesis that the human population can be racially carved

genetically with precision and that such carving can serve a predictive function in medical contexts. However, genomics and molecular studies often debunk this hypothesis [Cooper et al. (2003)]. For instance, in the case of HCV (hepatitis C virus infection), it had long been noted that medical treatment of individuals of self-professed African ancestry was less successful than treatment of individuals of self-professed Caucasian and Asian descent. The reason seems to be that individuals of African origin more often – but not universally – possess (compared to Caucasian and Asian individuals) a DNA sequence (i.e., *IL28B*) coding for a protein (i.e., interferon-λ-3) that plays a disruptive role when HCV treatments are administered. Thus "The profile based on race to predict treatment success rate in the past is now proven to be overly simplified. It is actually the *IL28B* genotype that plays a major role in determining treatment response, not ethnicity…." [Fan Lu et al. (2014), p. 8]. What we would like to highlight in this case is the interplay between the sophisticated statistical analysis of the genome wide association studies and the theoretically-rich understanding of an immunological mechanism at the molecular level, that is, in a way, the transition from statistically-based race medicine to a molecular understanding that is more in line with the ethos of personalised medicine.

III.3 *Observational evidence*

Clinicians have experimented during the pandemic with a variety of treatments whose safety and relative effectiveness should, it goes without saying, eventually be justified through RCTs.[6] Nonetheless, as we said in the previous sub-section, the division of medical labour heavily relies on the temporal primacy of theoretical and clinical insights. Given their privileged knowledge of the interaction between humans and pathogens, clinicians can thus hypothesise the efficacy of a medical intervention and the nature of the relationships between different classes of patients and disease. The pandemic case offers a test for such medical practices of course.

Cohort studies in particular, which have been disparaged by overzealous evidence-based medicine supporters [Cohen et al. (2004), p. 38], play a clear role in devising medical interventions. For instance, in one cohort study it was tested whether Tocilizumab might be an effective treatment for severely ill Covid-19 patients [Guaraldi et al. (2020)]. Studies of such kind are preliminary to RCTs, further demonstrating the role of theoretical and clinical insights in medicine. In another study, it was tested whether the lethality of Sars-CoV-2 had decreased over time [Flacco et al. (2020)]. This study – whose rationale was clinical (i.e., the observation that the virulence of the virus had diminished over time given the difference in

viral load between the testing swabs collected, respectively, in March and May, in Italian hospitals) – might be important to revise the inputs of epidemiological models. However, 'low-quality' evidence of this kind is often dismissed in the spirit of evidential prioritisation and hierarchisation.

III.4 *Mechanistic evidence*

The history of medicine points to the primary causal role of mechanistic reasoning and evidence. Take the HIV global epidemic (or pandemic). The breakthrough in managing the global epidemic did not come from statistical analysis or epidemiological modelling, but thanks to mechanistic studies. Mechanistic research underpinned by conceptual models and hypotheses coming from virology, immunology and molecular biology allowed the targeted search for drugs that could be used in order to inhibit the virus' life cycle in a variety of ways: its entry in the cell, the proliferation of its RNA in the cytoplasm, the integration of its genome within the host's genome etc. For instance, the first drug developed (i.e., AZT, a nucleoside reverse transcriptase inhibitor) targeted the reverse transcription capabilities of the virus. The rationale of our capacity to manage the HIV global epidemic is that mechanistic science has allowed the generation of a therapy with antiretroviral drugs: instead of nullifying the presence of the virus in the organism, and in the absence of a vaccine, we reduce its viral load, transforming a viral infection that was initially a death sentence into a chronic condition.

In analogy with the HIV case, mechanistic research should play a prominent role in the case of the current pandemic. Putative knowledge about the ways in which cellular infection and responses occur as well as the ways infection and response are mediated by organismal constituents (e.g., proteins, antibodies, T-cells) potentially leads to appropriate medical interventions. A thoroughly mechanistic understanding of Sars-CoV-2 interaction with organismal hosts is at the basis of the experimentation with Remdesivir. The extemporaneous treatment trialled by clinicians in the early phases of the pandemic is ultimately motivated by the theoretical conceptualisation of the drug's action and its potential to disrupt the virus' life cycle. Even though we do not know much about Sars-CoV-2, we know it's a coronavirus – for which, significantly, there were until the end of 2020 no available vaccines – and we have sequenced its genome. On this basis, we can make inferences about its life cycle and the proteins it uses in order to infect the human hosts. This knowledge allows to conceptualise mechanistically the ways in which the virus infects cells and replicates and, as a consequence, to devise potential medical interventions (Figure 3).

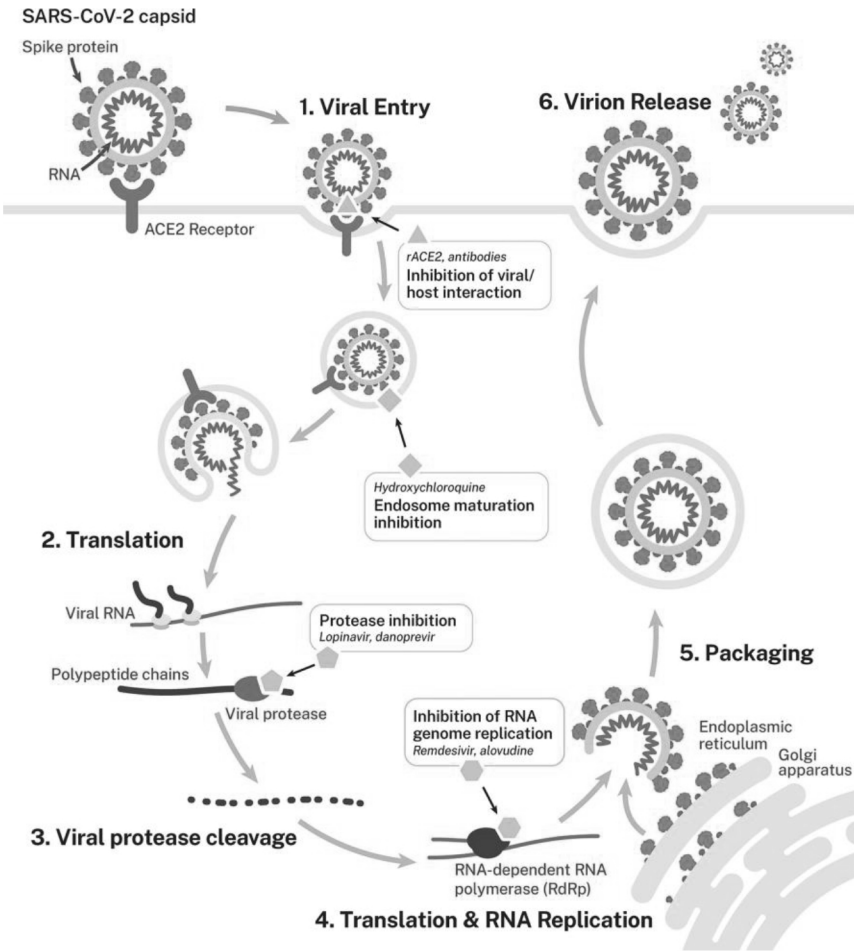


Figure 3 – Sars-CoV-2 life cycle and possible medical interventions [from Eastman et al. (2020)].

On the basis of this mechanistic conceptualisation, it was postulated that Remdesivir could be an effective medical intervention. This treatment acts by causing an inhibition of transcription (and hence virus replication). Remdesivir is an artificial substance that, following administration through intravenous injection to the patient, passes through the cellular membrane and diffuses into the cell's cytoplasm, where it is eventually processed by the cell (in a way that is not totally understood in mechanistic detail) in or-

der to produce a nucleoside triphosphate that is eventually recruited by the viral RNA polymerase. The upshot is that the viral RNA polymerase is tricked into recruiting an artificial analogue of a natural nucleoside triphosphate, but such recruitment slows down transcription by delaying chain termination. Remdesivir is hypothesised to interact with a specific residue of the RNA polymerase. Furthermore, Remdesivir only disrupts viral – but not human - transcription because human RNA polymerases do not recruit it. This means that human physiological processes are not impaired.

Mechanistic studies of this kind are arguably the best prospect we have to manage through medical interventions this pandemic. As Eastman et al. (2020), p. 680, claim "Repurposing or repositioning an effective small-molecule therapeutic promises to be the fastest therapeutic means to stem the tide of the pandemic."

III.5 *Integration*

The current pandemic clearly shows, in our opinion, that a truly evidence-based medicine must integrate computational, statistical and non-statistical sources of medical information and that this requires, in the end, also qualitative evidence clinically gathered concerning single patients, cohorts and, arguably most importantly, evidence concerning the mechanisms underlying the physiological and immunological responses of single patients over which inductive generalisations can be founded. By integration we refer to the reciprocal influence that different kinds of evidence have on the generation, refinement and testing of the hypotheses formulated by using different methodologies. Let us give some examples.

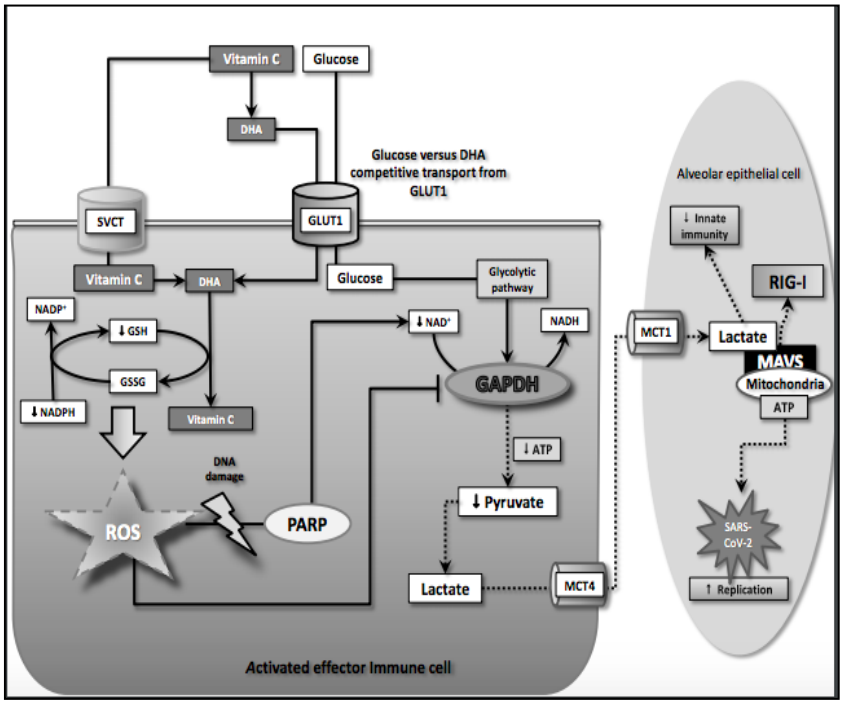
The causal role of asymptomatic patients in transmission had been grossly underestimated as an artefact of the influenza model originally chosen as the basis of the Imperial College London simulator, but several clinical [Lavezzo et al. (2020)] and statistical studies [Beale et al. (2020)] have indicated that asymptomatic patients are much more common that originally thought; the non-pharmaceutical interventions proposed to curb transmission on this basis were ineffective (for instance leading to neglecting the testing of nurses working in several care homes) and modelling has been refined as a consequence. Mechanistic evidence can also contribute to testing the efficacy of the non pharmaceutical interventions extrapolated from computational models. For instance, if long lasting protective immunity to Sars-CoV-2 turns out to be also dependent on T-cell responses and not merely antibodies [Sekine et al. (2020)], a mechanistic insight would contribute to explaining the inefficacy of certain kinds of restrictions (e.g., clos-

ing schools). Several kinds of evidence (clinical, statistical and mechanistic) thus heavily inform modelling and the testing of modelling predictions.

Analogously, statistical studies cannot per se be an appropriate basis for the needed non-pharmaceutical and medical interventions to come out of the current pandemic for a variety of reasons. First, statistical studies are often temporally and epistemologically parasitic on the theoretical insights provided by mechanistic reasoning and clinical evidence. Secondly, as we already anticipated in section III.2, testing the hypothesis concerning the effectiveness of a medical intervention gathered through an RCT often requires mechanistic evidence. The reason is that the hypothesis is relative to the population of reference used in the RCT but cannot be extrapolated indiscriminately to, for instance, all individual patients. The translation of the populational effectiveness of a drug to the individual might require more refined population stratification on the basis of mechanistic knowledge (as the race medicine case illustrated in section III.2 shows). At the same time, RCTs are necessary to test the populational effectiveness of medical interventions. In this respect, it goes without saying that Remdesivir's effectiveness is not merely mechanistically justifiable. In fact, at least 10 global clinical trials are currently registered [Eastman et al. (2020), cf. figure 4 and table 1].[7] This means, more generally, that the so-called 'low-quality' evidence coming from cohort and other qualitative and observational studies should be assessed according to stringent statistical parameters instead of being dismissed in the spirit of evidential prioritisation and hierarchisation. The same applies to mechanistic evidence. It would be preposterous to dismiss mechanistic evidence as necessarily local and organism-specific. The inductive extrapolation basis of mechanistic studies is founded on the similarities between varieties of biological entities: by assumption, most human cells are similar enough to allow diffusion of Remdesivir and most Sars-CoV-2 viruses are similar enough to use an RNA polymerase for transcription. Given these biological similarities, local mechanistic explanations become amenable to be generalisable. At the same time, while experimentation in vivo is of course key to such studies, RCTs are necessary. Their calibration is essential.

An illustrative example of integration of evidences concerns the testing of the medical benefits of vitamin C administration to Covid-19 patients. On the one hand, physiological pathways have been analysed in order to mechanistically conceptualise how vitamin C might counteract the infection. Erol (2020) draws a typical mechanistic diagram showing how vitamin C acts within the body (Figure 4-top). On the other hand, a RCT aimed to investigate the effectiveness of vitamin C administration in the case of Sars-CoV-2

patients developing pneumonia has begun in Wuhan, China [Carr (2020)]. Figure 4-BOTTOM shows the parameters of this typical trial.



Study Design Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	140 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Triple (Participant, Care Provider, Outcomes Assessor)
Primary Purpose:	Treatment
Official Title:	Vitamin C Infusion for the Treatment of Severe 2019-nCoV Infected Pneumonia: a Prospective Randomized Clinical Trial
Actual Study Start Date :	February 14, 2020
Estimated Primary Completion Date :	September 30, 2020
Estimated Study Completion Date :	September 30, 2020

Resource links provided by the National Library of Medicine NIH NLM

MedlinePlus related topics: Pneumonia Vitamin C

Drug Information available for: Ascorbic acid Sodium ascorbate Magnesium ascorbate

U.S. FDA Resources

Figure 4 – (TOP) Mechanistic description of action of vitamin C against Covid-19 virus [from Erol (2020)]. (BOTTOM) Clinical trial description and parameters [Carr (2020)].

Another example concerns the use of plasma from recovered patients to supply antibodies to infected patients. Presented as a successful treatment in some hospitals in Northern Italy,[8] it has been put into doubt by a recent RTC [Li, Zhang, Hu et al. (2020)].

Importantly, integration is not unidirectional (in the sense, for instance, that statistical studies provide the basis to test mechanistic and observational 'low-quality' hypotheses but not vice-versa) but multidirectional. An enlightening example of multidirectional evidential integration is the study by Garvin et al. (2020). First, the gene expression patterns relative to Covid-19 patients' bronchoalveolar lavage fluid cells are compared to the same type of cells from a control group. Gene expression data provide crucial information concerning the molecular resources (e.g., proteins) used by the cells of the organism in response to viral infection. A supercomputer is used to analyse this data set. Given that we already possess a mechanistic model of good cellular physiology (in itself a statistical construct based on what is common to 'good' cells' physiological behaviour), on the basis of the analysed gene expression data it can be inferred that certain kinds of disruption to the normal physiological pathways might be correlated to disease. On this partially computational, statistical and mechanistic basis, the authors propose that the peptide bradykinin plays a crucial role in infection and that the 'bradykinin storm' (basically an overproduction of this peptide) is at the basis of many Covid-19 symptoms. Thirdly, the authors of this study identify some already approved drugs that might potentially defuse the 'bradykinin storm', proposing RCTs to test their effectiveness for Covid-19. In brief, several types of evidence fuel the various stages of a study adopting a multiplicity of methodologies. In the end, to consider such studies exemplars of statistical or mechanistic science seems to us meaningless.

The desperate need for integration in the current pandemic case is in our opinion just common-sensical, especially given the variety of medically relevant issues that need to be tackled (Figure 1) and the multifarious nature of the interventions that need to be devised by policy makers in order to manage the pandemic.

IV. Evidence Integration Improves Pandemic Management

We started by highlighting that many medically relevant aspects of the pandemic should be tackled in order to manage its course effectively. In order to do so, we can rely, as we have shown, on a multiplicity of

kinds of evidence. Indeed, evidence related to the four medically relevant aspects of Covid-19 is in some cases abundant. In this situation, the appeal by decision-makers to 'evidence-based' policies is partially ironic and partially worrying. It is partially ironic because, for instance, both Sweden's and other European countries' strategies were – initially – in many ways opposite to each other but, nominally, equally 'science-based'. More importantly for our argument, it is partially worrying because, despite appearing as a sound approach at first sight, evidence-based policy-making is problematic when framed in terms of evidence prioritisation. To some researchers, contemporary biomedical science seems to be especially focused on statistical studies and probabilistic modelling, at the expense of mechanistic and observational evidence. Following this provocative interpretation, it could be argued that the current pandemic clearly exhibits the lurking clash between, on the one hand, 'statistical technocrats' [Charlton & Miles (1998)] with their smug prioritisation of medical evidence and, on the other, 'old-fashioned' clinicians and mechanistic scientists whose focus is on the causal interaction between the patient-organism and the disease-pathogen. We do not believe that statistical technocrats want to rule the world. At the same time, when the bias in favour of statistical evidence is formalised by the use of hierarchies, there are reasons to be worried. We argued that evidence prioritisation is problematic, impoverishes biomedical research and, as we shall relate briefly, impairs policy-making. The alternative we propose is evidence integration, an approach that, instead of prioritising types of evidence on the basis of potential bias, aims to enhance the reciprocal influence that different kinds of evidence have on the generation, refinement and testing of the hypotheses formulated by using different methodologies. This approach has the virtue of respecting the richness of the biomedical sciences, including the paramount role played by clinical research, small-scale observational studies and mechanistic research. We illustrated several examples of evidence integration in section III.5. We also tried to show that many studies are, as a matter of fact, multi-methodological, giving further reasons to think that the lurking clash between technocrats and mechanistic scientists might, as a matter of fact, amount to an overinterpretation.

We would now like to argue that evidence integration is important for policy making for the following reasons. The first is obvious. Given that the management of the pandemic requires different kinds of interventions, focus on one type of evidence is simplistic. In this respect, modelling is important for studying and controlling transmission, that is,

devising non-pharmaceutical interventions; conversely, mechanistic studies and observational surveys are more important to devise pharmaceutical interventions which will be sanctioned in terms of safety and population effectiveness by RCTs. This is a trivial point that, however, should not be forgotten as it shows that the division of medical labour is essential and that the relevance of a type of evidence is correlated to the medical aspect of interest and the kind of intervention sought. Most importantly, as we have extensively shown in section III.5, the significance of all kinds of evidence influences all other kinds of research, be it by refining models, triggering RCTs or testing mechanistic hypotheses. It seems to us unreasonable to regard a kind of evidence as superior, particularly when such prioritisation judgement is independent of the kind of intervention taken into consideration.

The second point we would like to make concerns the role of governments. Simplistically, it could be argued that devising pharmaceutical interventions is not the province of governments' action, as such role lies purely on 'self-organising' science. This idealistic picture of value-free science becomes particularly problematic during the current pandemic, which has seen an unprecedented – and in our opinion ethically justifiable – level of governmental intervention on scientific research. Readdressing scientific agendas can be done in several different ways. What we suggest is that governments should play such role in a balanced way, in at least two respects. In a first respect, it should not be biased by being implicitly based on evidence prioritisation. Take as an example the idiosyncratic policies concerning the use of face masks: there is a lack of RCTs concerning their effectiveness [MacIntyre and Chughtai (2015)], but their mandatory use has been locally justified through experts' opinions and folk-mechanistic understanding of how the virus spreads. A governmental intervention might transform this folk-mechanistic knowledge into good evidence, for instance by funding an engineering study. Another possible area of intervention – among an indefinite set – is financing the development of more reliable and comprehensive antigenic tests, in which case mechanistic knowledge is essential. In the second respect, governments' power to readdress scientific agendas should be balanced in the sense of not being biased to seek only non-pharmaceutical interventions. Of course, most governments have directed substantial amounts of public money to vaccine research, considered one of the most promising pharmaceutical interventions. And many governments have directly funded extensive RCT programmes for already available drugs. However, given their power in readdressing the scientific agenda

with directed funding programmes, when eventually the emphasis on transmission control wears off, the more the need to invest in mechanistic research is justified. In case vaccines in development and already available drugs turn out to be ineffective, drug development will necessarily have to rely on fundamental mechanistic research in pathophysiology and immunology.

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AUTHORS' NOTE

This article was written in July 2020. Our understanding of the Covid-19 disease has substantially increased since then. Therefore, the reader might find some references and examples outdated. Nevertheless, the authors believe that the article's general argument and conclusions still stand.

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NOTES

[1] *www.gradeworkinggroup.org*

[2] A text-book example of confounding variable is atmospheric pressure, whose reduction causes at the same time the fall in barometer reading and the storm: a pure statistical analysis would consider changes in barometer reading as difference-making causes with respect to weather.

[3] *https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/*, data retrieved June 26th, 2020.

[4] The probabilistic interpretation of causality has a long tradition in English philosophy. It started at least with Hume's 'Treatise' and was formalised in Stuart Mill's 'Logic', whose method looks for regularities allowing predictions,

and not for the causes of the effects behind these regularities. An interesting analysis of this tradition is found in Gadamer's 'Truth and Method', section I.1.a

[5] *https://www.nature.com/articles/d41586-020-01824-5*

[6] However, as we argue more in detail in 3.5, this does not mean that their relative effectiveness at the population level can be translated to their effectiveness at the individual patient level or to a population with different characteristics (e.g., the external validity problem, see section 2).

[7] An interim trial-result by the WHO seems to refute the hypothesis that Remdesivir is an effective drug for Covid-19 treatment. Nonetheless, the US Food and Drug Administration has approved it. (*https://www.nejm.org/doi/full/10.1056/NEJMoa2007764*)

[8] *https://isbtweb.org/fileadmin/user_upload/Italy.pdf*, retrieved July 4th, 2020.

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